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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,119	05/31/2007	Kazuo Shinya	039371-20	8925

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EXAMINER	
YAKOVLEVA, GALINA M	
ART UNIT	PAPER NUMBER
1641	

NOTIFICATION DATE	DELIVERY MODE
03/31/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/594,119	SHINYA ET AL.	
	Examiner	Art Unit	
	GALINA YAKOVLEVA	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2011 and 21 March 2011 and22*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-39,41 and 42* is/are pending in the application.

4a) Of the above claim(s) *19-27,29-31,34 and 35* is/are withdrawn from consideration.

5)☒ Claim(s) *28,36-38 and 41* is/are allowed.

6)☒ Claim(s) *32,33 and 39* is/are rejected.

7)☒ Claim(s) *42* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03/16/2011*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner charged with the present case has changed. See contact information below. Responsive to communications entered 02/28/2011 (Reply to the Office Action), 03/21/2011 (Supplemental Amendment) and 03/22/2011 (Second Supplemental Amendment).

Status of Claims

Claims 1-18 and 40 are cancelled. Claims 19-39 and 41-42 are pending. Claims 19-27, 29-31, 34 and 35 are withdrawn. Claims 28, 32, 33, 36-39, 41 and 42 are examined.

Priority

The instant application, Pub. No. US 2007/0287152 A1, is a 371 filing of PCT/JP05/06077 filed 03/30/2005, which claims foreign priority to JP 2004-102879 filed 03/31/2004 and JP 2004-112335 filed 04/06/2004.

Information Disclosure Statement

The information disclosure statement, submitted on 03/16/2011, is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

The objection to the information disclosure statement, filed 09/25/2006, as not complying with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 is withdrawn, and the IDS has been fully considered.

With regard to the information disclosure statement, filed 07/29/2007, Applicant indicated that the publication date of reference 1 is June 2000, and the Supplemental

IDS will follow. Although, the Supplemental IDS for this reference has not been filed, the Office is considering this reference and will enter the indicated publication date for Applicant.

Withdrawn Objections/Rejections

I. The objection to the oath/declaration is withdrawn in view of Applicant's amendment of the oath/declaration.

II. The objection to the drawings is withdrawn in view of Applicant's amendment of the drawings.

III. The objection to the abstract is withdrawn in view of Applicant's amendment of the abstract.

IV. The rejection of Claims 28 and 32-33 under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn in view of Applicant's amendment of the claims.

V. The rejection of Claims 28 and 32-33 under 35 U.S.C. 102(e) as being anticipated by U.S. Patent App. Pub. No. 2006/0234229 to Van Beuningen *et al.*, is withdrawn in view of Applicant's amendment of the claims and arguments.

Claim Objections

Claim 42 is objected to because of the following informalities: Claim 42 recites an amino acid that falls within the nucleotide/amino acid sequence rules and must therefore be identified by a sequence identifier number in the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32, 33 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for lack of antecedent basis and use of unclear wording.

For Applicant's convenience, in the claims, the examiner's comments/suggestions are provided in parentheses, and the elements, which lack antecedent basis and/or unclear, are emphasized.

32. A method for capturing an intracellular biological substance comprising:

recovering *an* (the) intracellular biological substance by a method comprising:

at least the following:

(i) producing a chimeric substance, which comprises a probe substance, except a peptide or protein, capable of interacting with the (intracellular) biological substance, an epitope tag peptide recognized by an antibody and an organic compound having a chemical structure capable of binding to both the probe substance and the epitope tag (peptide), the chimeric substance produced by labeling *a* (the) probe substance, except a peptide or protein, capable of interacting with the (intracellular) biological substance, via one terminal functional group of *an* (the) organic compound with a labeling substance comprising the organic compound and *an* (the) epitope tag peptide bound to the organic compound (which epitope tag peptide is) capable of being specifically recognized by *an* (the) antibody,

(ii) introducing the chimeric substance into a cell,

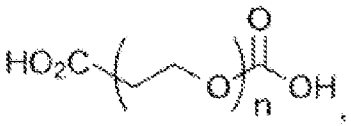
(iii) enabling interaction between the probe substance in the chimeric substance and the intracellular biological substance, and

(iv) removing a complex of the intracellular biological substance and the chimeric substance obtained through the interaction from the cell, and subsequently capturing the recovered intracellular biological substance comprising at least the following:

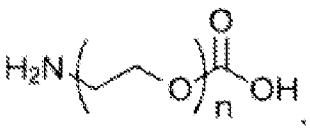
(A) guiding a sample solution containing the complex of the intracellular biological substance and the chimeric substance to a region of a solid surface;

(B) enabling the interaction of said antibody immobilized to the solid surface with the epitope tag peptide in the chimeric substance included in the complex.

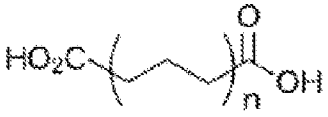
39. A method described in claim 32, wherein the *labeling substance* (organic compound; See paragraphs [0060]-[0063] of the instant application, Pub. No. US 2007/0287152 A1, wherein the compounds listed below are identified as the organic compounds) is a compound of formula



a compound of formula,



a compound of formula,



or a compound of formula

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32, 33 and 39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for capturing an intracellular biological substance in disrupted cells, does not reasonably provide enablement for capturing an intracellular biological substance in intact cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

There are many factors be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether undue experiment is necessitated. These factors can include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the relative skill of those in the art;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1 and 2) The breadth of the claims and the nature of the invention: Claims 32, 33 and 39, as recited in independent Claim 32, are drawn to a method for capturing an intracellular biological substance. Per the Applicant's Reply entered 02/28/2011, Claim 32 has been amended to recite, *inter alia*, "(ii) introducing the chimeric substance into a

cell, (iii) enabling interaction between the probe substance in the chimeric substance and the intracellular biological substance, and (iv) removing a complex of the intracellular biological substance and the chimeric substance obtained through the interaction from the cell." Thus, the claims imply that the recited chimeric substances are capable to penetrate into the cells, interact with the intracellular biological substance within the intact cells to form a complex, which can be removed form the cells, and subsequently captured by an antibody.

(3 and 5) The state of the prior art and the level of predictability in the art: The art recognizes the difficulties with assessing the cell permeability of synthetic molecules. As stated, for example, in Introduction of Yu *et al.*, "A high-throughput assay for assessing the cell permeability of combinatorial libraries," *Nature Biotechnology,* 2005, vol. 23, No. 6, pp. 746-751, peptides are poorly cell permeable and sensitive to proteases.

(4) The level of one or ordinary skill: The level of skill in the art would be high, most likely at the Ph.D. level. However, such persons of ordinary skill in this art, *given its unpredictability*, would have to engage in undue (non-routine) experimentation to carry out the invention as claimed.

(6-7) The amount of direction provided by the inventor and the existence of working examples: The specification has provided guidance for capturing an intracellular biological substance in the supernatants of the disrupted cells (Examples 2, paragraph [0137] of the instant application, Pub. No. US 2007/0287152 A1). However, the specification lacks any description of methods for introducing a chimeric substance

into a cell, forming a complex of the chimeric substance with an intracellular biological substance within the intact cell and removing the complex of the intracellular biological substance and the chimeric substance from the cell.

(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: The claims contain only recitation of of methods for introducing a chimeric substance into a cell, forming a complex between the chimeric substance and an intracellular biological substance within the intact cell and removing the complex of the intracellular biological substance and the chimeric substance from the cell. However, the instant specification does not provide to one skilled in the art a reasonable amount of guidance with respect to the direction in which the experimentation should proceed in carrying out the full scope of the claimed invention. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 and n.23, 20 USPQ2d 1438, 1455 and n.23 (Fed. Cir. 1991). Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed. Thus, due to the inadequacies of the instant disclosure, undue experimentation would be required of one of ordinary skill in the art to practice the full scope of the claimed invention.

Allowable Subject Matter

Claims 28, 36-38, 41 and 42 are allowed because the prior art does not teach or fairly suggest a method for capturing a biological substance comprising at least the

following: (A) guiding a sample solution containing a complex of the biological substance and a chimeric substance to a region of a solid surface, the chimeric substance comprising a probe substance, except a peptide or protein, capable of interacting with the biological substance, an epitope tag peptide recognized by an antibody, which antibody is immobilized to a solid surface, and an organic compound having a chemical structure capable of binding to both the probe substance and the epitope tag peptide; (B) enabling the interaction of said antibody immobilized to the solid surface with the epitope tag peptide in the chimeric substance included in the complex.

The chimeric substance of the instant invention functions as a reversibly detachable bridge between a biological substance to be captured and an antibody immobilized on the solid surface. The reversibly detachable bridge makes it possible to dissociate, dilute and recover the biological substance.

The avidin-biotin binding system is well-known in the art. See, for example, U.S. Patent App. Pub. No. 2006/0234229 to Van Beuningen *et al.* (of record).

The fused protein-epitope tag peptide technology, also well-known in the art, is based on construction of a fusion protein with an epitope tag peptide, such as a FLAG affinity tag. See, for example, Einhauer, A.; Jungbauer, A.; "The FLAG peptide, a versatile fusion tag for the purification of recombinant proteins", Journal of Biochemical and Biophysical Methods, 2001, vol. 49, pp.455-465 (IDS entered 06/12/209). A small FLAG sequence is cloned into the protein under study. The sequence binds to immobilized antibody directed against the FLAG sequence. After some washing steps,

elution is effected with a peptide that competes for binding site on an anti-FLAG antibody.

Conclusion

Claims 28, 36-38, 41 are allowed. Claims 32, 33 and 39 are rejected. Claim 42 is objected to.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GALINA YAKOVLEVA whose telephone number is (571)270-3282. The examiner can normally be reached on Monday-Friday 8:00 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached on (571)272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/G. Y./
Examiner, Art Unit 1641

/Mark L. Shibuya/
Supervisory Patent Examiner, Art Unit 1641